Amendments to the specification:

Please replace Abstract appearing on page 40 with the following:

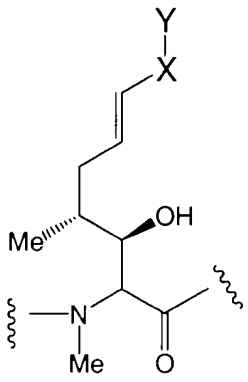
Abstract

The present invention relates to a cyclosporin analog of the following formula (I) or a pro-drug or pharmaceutically acceptable salt thereof:

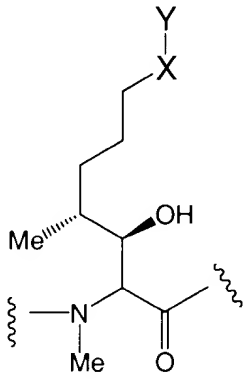
A---B---Sar-MeLeu-Val-MeLeu-Ala---U---MeLeu-MeLeu-MeVal
1 2 8

(I)

In particular, residue A maybe represented by either formula A1 or A2 as illustrated below:



or



(A1) (A2)

where X ~~is absent, -C1-C6-alkyl- or -C3-C6-cycloalkyl-;~~ and Y ~~is~~ are defined herein. ~~selected from the groups: aryl, substituted aryl, heteroaryl, and substituted heteroaryl; residue B is -αAbu-, -Val-, -Thr- or -Nva-; and residue U is -(D)Ala-, -(D)Ser-, -[O-(2-hydroxyethyl)(D)Ser]-, -[O-acyl(D)Ser]- or -[O-(2-acyloxyethyl)(D)Ser]-.~~ In a second embodiment, the present invention relates to ~~the use of the cyclosporin analogs of the present invention or a pro-drug or pharmaceutically acceptable salt thereof in~~ pharmaceutical compositions comprising pro-

drugs or pharmaceutically acceptable salts of the compounds of the present invention and the use thereof for ~~the treatment~~ treating ~~of~~ autoimmune diseases or for the prevention of organ transplantation rejection in a subject. In a third embodiment, the present invention relates to processes for the production of novel cyclosporin analogs of the present invention. ~~The present invention also contemplates method(s) of treatment of autoimmune diseases or prevention of organ transplant rejection in a subject by administering to the subject therapeutically effective amounts of the cyclosporin analogs of the present invention with or without the concurrent use of other drugs or pharmaceutically acceptable carriers or excipients.~~

Please amend the paragraph beginning on page 7, line 34 as follows:

The potent immunomodulatory activity which compounds of the instant invention demonstrate in common *in vitro* biological assays (for example, calcineurine assay, nuclear factor of activated T cells (NFAT) reporter gene assay, murine and human mixed lymphocyte reaction) or animal models (for example delayed-type hypersensitivity response - DTH, popliteal lymph node assay - PLN) indicate that these compounds possess immunosuppressive, antimicrobial, antifungal, antiviral, antiinflammatory, and antiproliferative activity, and possess the ability to reverse chemotherapeutic drug resistance. As agents block T-cell activation, a prerequisite for human immunodeficiency virus (HIV) proliferation, the compounds are useful as prophylactics for the prevention of HIV replication. The compounds of the invention would be useful when used alone, or in combination therapy with other immunosuppressants, for example, but not limited to, FK506, rapamycin, cyclosporin A, picibanil, mycophenolic acid, azathioprine, prednisolone, cyclophosphamide, brequinar and leflunomide.

Please amend the paragraph beginning on page 8, line 28 as follows:

Further uses include the treatment and prophylaxis of inflammatory and hyperproliferative skin diseases and cutaneous manifestations of immunologically-mediated illnesses, such as psoriasis, atopical dermatitis, contact dermatitis and further eczematous

dermatitises, seborrhoeis dermatitis, Lichen planus, Pemphigus, bullous pemphigoid, Epidermolysis bullosa, urticaria, angioedemas, vasculitides, erythemas, cutaneous eosinophilias, Lupus erythematosus, acne and Alopecia areata; various eye diseases (autoimmune and otherwise) such as keratoconjunctivitis, vernal conjunctivitis, keratitis, herpetic keratitis, conical cornea, dystrophia epithelialis corneae, corneal leukoma, ocular pemphigus, Mooren's ulcer, Scleritis, Graves' opthalmopathy, Vogt-Koyanagi-Harada syndrome, sarcoidosis, multiple myeloma, etc.; obstructive airway diseases, which includes conditions such as chronic obstructive pulmonary disease (COPD) asthma (for example, bronchial asthma, allergic asthma, intrinsic asthma, extrinsic asthma and dust asthma), particularly chronic or inveterate asthma (for example, late asthma and airway hyper-responsiveness), bronchitis, allergic rhinitis and the like; inflammation of mucosa and blood vessels such as gastric ulcers, vascular damage caused by ischemic diseases and thrombosis. Moreover, hyperproliferative vascular diseases such as intimal smooth muscle cell hyperplasia, restenosis and vascular occlusion, particularly following biologically- or mechanically-mediated vascular injury can be treated or prevented by the compounds of the invention.

Please amend the paragraph beginning on page 9, line 12 as follows:

Other treatable conditions would include but are not limited to ischemic bowel diseases, inflammatory bowel diseases, necrotizing enterocolitis, intestinal lesions associated with thermal burns and leukotriene B_4-mediated diseases; intestinal inflammations/allergies such as Coeliac diseases, proctitis, eosinophilic gastroenteritis, mastocytosis, Crohn's disease and ulcerative colitis; food-related allergic diseases which have symptomatic manifestation remote from the gastro-intestinal tract (e.g., migraine, rhinitis and eczema); renal diseases such as interstitial nephritis, Goodpasture's syndrome, hemolytic-uremic syndrome and diabetic nephropathy; nervous diseases such as multiple myositis, Guillain-Barre syndrome, Meniere's disease, polyneuritis, multiple neuritis, mononeuritis and radiculopathy; endocrine diseases such as hyperthyroidism and Basedow's disease; hematic diseases such as pure red cell aplasia, aplastic anemia, hypoplastic anemia, idiopathic

thrombocytopenic purpura, autoimmune hemolytic anemia, agranulocytosis, pernicious anemia, megaloblastic anemia and anerythroplasia; bone diseases such as osteoporosis; respiratory diseases such as sarcoidosis, fibroid lung and idiopathic interstitial pneumonia; skin disease such as dermatomyositis, leukoderma vulgaris, ichthyosis vulgaris, photoallergic sensitivity and cutaneous T cell lymphoma; circulatory diseases such as arteriosclerosis, atherosclerosis, aortitis syndrome, polyarteritis nodosa and myocardosis; collagen diseases such as scleroderma, Wegener's granuloma and Sjogren's syndrome; adiposis; eosinophilic fasciitis; periodontal disease such as lesions of gingiva, periodontium, alveolar bone and substantia ossea dentis; nephrotic syndrome such as glomerulonephritis; male pattern aleopecia or alopecia senilis by preventing epilation or providing hair germination and/or promoting hair generation and hair growth; muscular dystrophy; Pyoderma and Sezary's syndrome; Addison's disease; active oxygen-mediated diseases, as for example organ injury such as ischemia-reperfusion injury of organs (such as heart, liver, kidney and digestive tract) which occurs upon preservation, transplantation or ischemic disease (for example, thrombosis and cardiac infraction): intestinal diseases such as endotoxin-shock, pseudomembranous colitis and colitis caused by drug or radiation; renal diseases such as ischemic acute renal insufficiency and chronic renal insufficiency; pulmonary diseases such as toxinosis caused by lung-oxygen or drug (for example, paracort and bleomycins), lung cancer and pulmonary emphysema; ocular diseases such as cataracta, siderosis, retinitis, pigmentosa, senile macular degeneration, vitreal scarring and corneal alkali burn; dermatitis such as erythema multiforme, linear IgA ballous dermatitis and cement dermatitis; and others such as gingivitis, periodontitis, sepsis, pancreatitis, diseases caused by environmental pollution (for example, air pollution), aging, carcinogenis, metastasis of carcinoma and hypobaropathy; disease caused by histamine or leukotriene-C_4 release; Behcet's disease such as intestinal-, vasculo- or neuro-Behcet's disease, and also Behcet's which affects the oral cavity, skin, eye, vulva, articulation, epididymis, lung, kidney and so on. Furthermore, the compounds of the invention are useful for the treatment and prevention of hepatic disease such as immunogenic diseases (for example, chronic autoimmune liver diseases such as the group consisting of autoimmune hepatitis, primary biliary cirrhosis and sclerosing

cholangitis), partial liver resection, acute liver necrosis (e.g., necrosis caused by toxin, viral hepatitis, shock or anoxia), B-virus hepatitis, non-A/non-B hepatitis, cirrhosis (such as alcoholic cirrhosis) and hepatic failure such as fulminant hepatic failure, late-onset hepatic failure and "acute-on-chronic" liver failure (acute liver failure on chronic liver diseases), and moreover are useful for various diseases because of their useful activity such as augmention of chemotherapeutic effect, preventing or treating activity of cytomegalovirus infection, particularly human cytomegalovirus (HCMV) infection, anti-inflammatory activity, and so on.

Please amend the paragraph beginning page 11, line 11 as follows:

Further, it has recently been shown that the steroid receptor-associated heat shock proteins (hsp or HSP), hsp56 or hsp59, belong to the class of immunophilin proteins (*see* "HSP70 induction by cyclosporin A in cultured rat hepatocytes: effect of vitamin E succinate," Andres, David et al., *Instituto de Bioqimica, Facultad de Farmacia, Universidad Complutense, Madrid, Spain.* J. Hepatol. (2000) 33(4), 570-579; "Cyclosporin A Induces an Atypical Heat Shock Response," Paslaru, Liliana, *et al.*, Unite de Genetique Moleculaire, Paris, Fr. Biochem. Biophys. Res. Commun. (2000), 269(2), 464-469; "The cyclosporine A –binding immunophilin CyP-40 and the FK506-binding immunophilin hsp56 bind to a common site on hsp90 and exist in independent cytosolic heterocomplexes with the untransformed glucocorticoid receptor," Owens-Grillo, Janet K. et al., Med. Sch., Univ. Michigan, Ann Arbor, MI USA. J. Biol. Chem. (1995), 270(35), 20479-84). The ability of a steroid receptor-associated heat shock protein to bind the immunosuppressive CsA suggests that the steroid receptor and immunophilin signal transduction pathways are functionally interrelated. The combined treatment of compounds of the present invention and low concentrations of a steroid ligand (for e.g., progesterone, dexamethasone) result in a significant enhancement of target gene expression over that seen in response to ligand alone. Thus, the compounds of the present invention potentiate steroid-mediated transactivation.

Please amend the paragraph beginning page 29, line 22 as follows:

Compounds in dimethyl sulfoxide (DMSO) (2.4µl) were added to a 96-well microplate and mixed with 50µl assay buffer (50mM Tris-HCl, pH 7.5; 100mM sodium chloride; 6mM magnesium chloride; 0.5mM dithiothreitol, 0.025% NP-40, 500µM calcium chloride, 0.27µM Calmodulin) containing 10µM Cyclophilin and 3nM Calcineurin. After warming to 37 °C for 60 mins, the enzymatic reaction was initiated by addition of phosphopeptide (7.5µl) to give a final concentration of 94µM. Phosphate release after 60 min at 37 °C was determined by addition of Biomol Green (100 µl) and measurement of the absorbance at 620nm after 15 mins at room temperature.

Please amend the paragraph beginning page 31, line 3 as follows:

NFAT activation follows precisely the activation of calcineurin by increased free calcium levels in the cytoplasm. Researchers from diverse fields are interested in the NFAT family of transcription factors, which are potential targets for newer and safer immunosuppressive drugs. In addition, the activation of NFAT proteins involves various cellular signal transduction pathways, including calcium mobilization and mitogen-activated protein kinase (MAP kinase) pathways linked to T-cell receptors and Ras1. To assist researchers probing the activity of NFAT proteins, Stratagene has developed a PathDetect cis-reporter plasmid, the pNFAT-Luc reporter plasmid (Stratagene, Inc. catalog # 219094), containing the NFAT binding site from the human IL-2 gene.2,7-9. The NFAT cis-reporting system includes the transfection-ready pNFAT-Luc reporter plasmid and the pCIS-CK negative control plasmid.

Please amend the paragraph beginning page 31, line 28 as follows:

Pharmacology studies have established that NFAT proteins can be activated by the protein kinase C activator phorbol ester (PMA) in combination with the calcium ionophore ionomycin, reagents that raise free intracellular calcium. When Jurkat cells, a mature human T-cell line, or Chinese hamster ovary cells (CHO cells) were transfected with the pNFAT-Luc plasmid and treated with 60 ng/ml of PMA and 1µg/ml of inomycin, luciferase activity

increased by 13- and 16-fold, respectively. Therefore, the enhancer element in the pNFAT-Luc plasmid is responsive to calcium mobilization. Cells transfected with pNFAT-Luc and then treated with either PMA or ionomycin alone did not show a significant increase in luciferase activity.

Please amend the paragraph beginning page 32, line 19 as follows:

Ca. $0.5x10^6$ lymphocytes from the spleen of female (8-10 weeks) Balb/c mice are incubated for 5 days in 0.2 ml cell growth medium with ca. 0.5×10^6 lymphocytes from the spleen of female (8-10 weeks) albino brown Agouti (CBA) mice. Test substance is added to the medium at various concentrations. Activity is assessed by ability to suppress proliferation-associated DNA synthesis as determined by incorporation of radiolabelled thymidine.

Please amend the paragraph beginning page 32, line 27 as follows:

Ca. 10^7 lymphocytes from the spleen of ~~OF1~~CF1, female mice are co-cultured with ca. $3x10^7$ sheep erythrocytes for 3 days. Test substance is added to the incubation medium in varying concentrations. Lymphocytes are harvested and plated onto agar with fresh sheep erythrocytes as antigen. Sensitized lymphocytes secrete antibody that coats the erythrocytes, which lyse to form a plaque in the presence of complement. Activity is assessed by reduction in the number of plaque forming, i.e., antibody product, cells.

Please amend the paragraph beginning page 29, line 22 as follows:

Efficacy of administered test substance is determined by bronchoalveolar lavage (BAL) and cell counting. For this purpose animals are sacrificed with Na pento-barbitone (100 mg/kg i.p.) and the trachea is exposed and cannulated. 5 successive 10 ml aliqots of Ca^2 + and Mg^2 + free Hank's balanced salt solution (HBSS), containing bovine serum albumin (BSA, 0.3%), EDTA (10mM) and 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid (HEPES) (10 mM) is then introduced into the lung and immediately aspirated by gentle compression of the lung tissue. Total cell counts in pooled eluates are determined using an

automatic cell counter. Lavage fluid is centrifuged at 200g for 10 minutes and the cell pellet resuspended in 1 ml of supplemented HBSS. 10 μl of this cell suspension is added to 190 μl of Turk's solution (1:20) dilution). Differential cell counts are made from smears stained by Diff-Quick. Cells are identified and counted under oil immersion (x1,000). A minimum of 500 cells per smear are counted and the total population of each cell type is calculated.